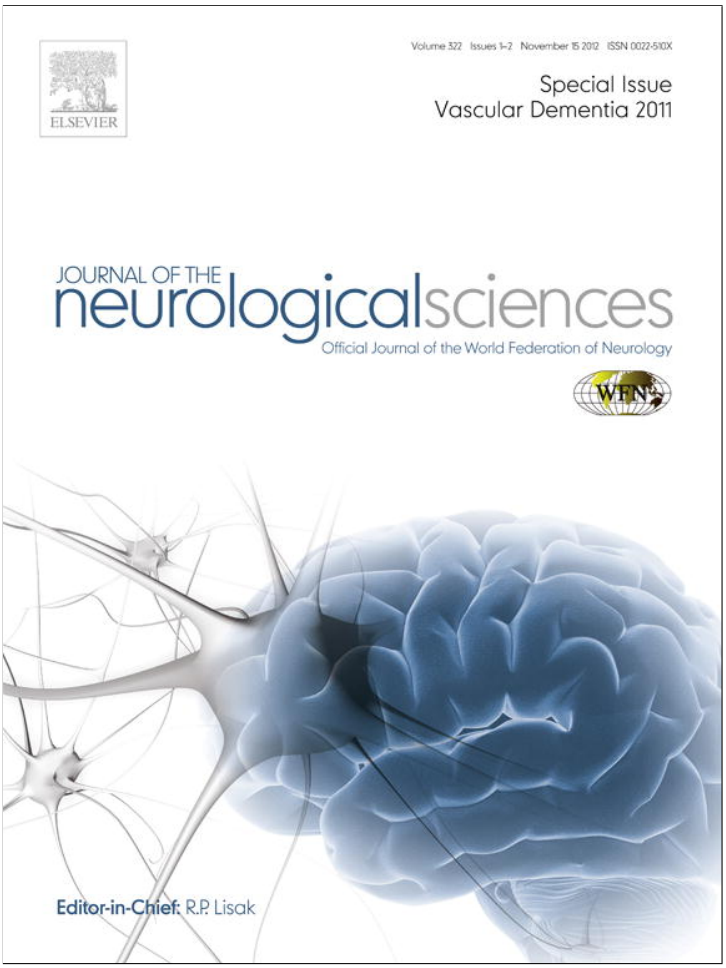

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The Spanish version of the Addenbrooke's Cognitive Examination — Revised (ACE-R) in subcortical ischemic vascular dementia

Catalina Raimondi [a], Ezequiel Gleichgerrcht [a,b,c], Pablo Richly [a], Teresa Torralva [a,b], María Roca [a,b], Julieta Camino [a], Facundo Manes [a,b,*]

[a] Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina
[b] Institute of Neuroscience, Favaloro University, Buenos Aires Argentina
[c] Laboratory of Neurosciences, Diego Portales University, Santiago 8370179, Chile

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ABSTRACT

Vascular dementia (VaD) is one of the most prevalent causes of dementia, and it is frequently misdiagnosed and undertreated in clinical practice. Because neuropsychological outcome depends, among other factors, on the size and location of the vascular brain injury, characterizing the cognitive profile of VaD has been especially challenging. Yet, there has been sufficient evidence to show a marked impairment of attention and executive functions, in particular in relation to Alzheimer disease. Being able to detect these deficits at bedside is crucial for everyday clinical practice, and yet, brief cognitive screening toots such as the Mini-Mental Sate Examination (MMSE) may overlook at cognitive deficits typical of patients with VaD. The Addenbrooke's Cognitive Examination Revised (ACE-R) is also a brief cognitive screening tool designed to incorporate the items of the MMSE and further extend the test to assess orientation, attention, verbal fluency, memory, language, and visuospatial abilities. In this study, we investigated the ability of the Spanish version of the ACE-R to detect the cognitive impairment showed in patients with subcortical ischemic vascular dementia, and we compared its usefulness to that of the MMSE in this population. Scores on these tests were compared to those of patients with Alzheimer disease and matched healthy controls. The 88-point cut-off proposed for the ACE-R was associated with a sensitivity of 100% and a specificity of 100% for the detection of cognitive impairment, demonstrating a stronger capacity than the MMSE (sensitivity of 42% with its 23-point cut-off score). We also found that the verbal fluency subtest of the ACE-R may be potentially useful in discriminating patients with subcortical ischemic vascular dementia from patients with AD. We discuss the utility of these findings in the context of everyday clinical practice and we propose that future studies should evaluate the potential usefulness of combining the ACE-R with a brief screening tool of executive functioning

1. Introduction

Cognitive impairment that is caused by, or associated with, vascular factors has been termed "vascular cognitive impairment" (VCI) [1]. Vascular cognitive impairment is one of the most prevalent causes of dementia, and is frequently misdiagnosed and undertreated in clinical practice. VCI includes all cases in which cognitive impairment is attributed to cerebrovascular disease and is greater than expected for normal aging. Vascular Dementia (VaD) is a subset of VCI, in which cognitive deficits are sufficiently severe to interfere with everyday social and occupational functioning. Nowadays, the recognition of a close relation between VaD and Alzheimer Disease is a field of growing interest. Recent studies suggest that 'pure' AD and 'pure' VaD are relatively uncommon, and that most elderly individuals with dementia have a combination of both AD pathology and cerebrovascular disease (AD with CVD) [2].

No single cognitive impairment profile characterizes VaD, especially because neuropsychological outcome depends, among other factors, on the size and location of the vascular brain injury. However, the involvement of vascular disease in dementia may produce a predominance of attention deficits and executive dysfunction (reflecting frontal lobe damage), while the memory impairment typically associated with AD may be less marked [3–6]. In fact, episodic memory is believed to be relatively spared in this population, especially compared with AD [7].

Current research in the field highlights the need of a screening test that identifies, at bedside, patients who may have a VaD, especially because full neuropsychological evaluation is not often available for every clinician in day-to-day clinical practice. Evidently, a screening test differs from a diagnostic test. A screening test is not intended to establish a diagnosis. Screening tests are usually applied to a population of individuals, often those at increased risk of having a particular disorder. Cognitive screenings commonly used to assess patients with

* Corresponding author at: Institute of Cognitive Neurology (INECO), Pacheco de Melo 1854, 1126 Buenos Aires, Argentina.
E-mail address: fmanes@ineco.org.ar (F. Manes).

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AD, such as the Mini Mental State Examination [8] which is sensitive to memory and speech disorders but insensitive to executive impairment, may not always provide suitable measures of the specific cognitive profile that characterize patients with VaD.

The Addenbrooke's Cognitive Examination (ACE) was developed with the aim of offering clinicians a brief and simple cognitive screening battery incorporating the MMSE, but extending it to cover a wider range of cognitive domains [9]. It consists of six subdomains assessing orientation, attention, verbal fluency, memory, language, and visuospatial abilities. It is more sensitive and reliable than the MMSE for the early detection of dementia in Alzheimer's disease and frontotemporal dementia [9,10]. The ACE has been used to assess cognitive impairment in other neuropsychiatric entities such as Parkinson's disease [11], corticobasal degeneration, progressive supranuclear palsy, other Parkinsonian syndromes [12,13],depression [14,15], and Vascular Dementia [16,17] among others. In 2006, the ACE was revised and data of this new version have been published by Mioshi et al. In this revised version, referred to as ACE-R, design changes were implemented to make the test easier to administrate, to facilitate cross-cultural usage, and to increase sensitivity and specificity [18]. To our knowledge, only one study from Korea used the ACE-R (K-ACER) to differentiate Alzheimer's disease (AD) from subcortical ischemic vascular dementia [19]. The aim of the present study was to investigate the ability of the Spanish version of the ACE-R to detect the cognitive impairment showed in VaD, and compare its usefulness to that of the MMSE in this population. The Spanish version of the ACE-R can be requested to the authors or accessed via www.fundacionineco.org.

2. Methods

2.1. Participants

A total of 83 subjects were included in this study, 26 of which were healthy controls, and 57 of which were diagnosed either with VaD (VC, $n=32$) or Alzheimer disease ($n=25$). Healthy controls had no history of either neurological or psychiatric disorder. All patients with VaD met the criteria for probable VaD formulated by the National Institute of Neurological Disorders (NINDS-AIREN) group [20]. All VaD subjects underwent head MRI and/or head CT, and had multiple lacunar infarcts of the basal gray matter and/or thalamus, in addition to periventricular and deep white matter lesions. Patients with AD diagnosis fulfilled NINCDS-ADRDA criteria [21]. All patients underwent a standard examination including neurological, neuropsychiatric evaluations and a head MRI and/or head CT, and their diagnoses were reviewed and confirm in the context of an interdisciplinary clinical meeting comprising neurologists, psychiatrists, neuropsychologists, and neuropsychiatrists. Severity of dementia was determined with the Clinical Dementia Rating (CDR). Patients with a CDR value of two points or higher were excluded from this study [22] in order to ensure that the data analyzed was derived from the early stages of each disorder. Presence of mood symptoms was determined using the Beck Depression Inventory II (BDI-II) [23] and only patients with a score of 13 points or below were included in the study.

2.2. Procedure

The study was initially approved by the ethics committee at the Institute of Cognitive Neurology (INECO) following international regulations established for human research subjects. For the purposes of this study, data was obtained from the Addenbrooke's Cognitive Examination — Revised [16] which also incorporates the Mini Mental State Examination (MMSE) [8]. The ACE-R evaluates six cognitive domains: orientation (10 points), attention (8 points), verbal fluency (14 points), memory (26 points), language (26 points), and visuospatial ability (16 points). ACE –R maximum score is 100, composed by the addition of all de domains. Average time needed to complete the ACE-R test is approximately 12–20 min, no special material is required.

2.3. Statistical analysis

Demographic and clinical information were compared between the groups using one-way ANOVAs with Bonferroni *post hoc* analyses when appropriate. When data was not normally distributed, U Mann–Whitney tests were used to compare two groups at a time. When analyzing categorical variables (e.g. gender), the Freeman–Halton extension of the Fisher exact probability test for 2×3 contingency tables was used.

In order to compare the usefulness of the MMSE and the ACE-R, we used receiver operating characteristic (ROC) curve analysis to determine sensitivity and specificity of each screening tool in its ability to distinguish (a) healthy controls and patients with dementia, and (b) patients with VaD from AD. The area under the ROC curve (AuC) was used as a measure of discriminatory accuracy, and the AuC values were compared between each other in order to test statistical differences following Hanley and McNeil (1983) algorithms. Correlations were sought between the total scores of the MMSE and ACE with the CDR using Spearman's correlation coefficient. All statistical analyses were performed using the PASW 18.0 statistical package and the α value was set at 0.05, two-tailed.

3. Results

The clinical and demographic profile of the groups is summarized in Table 1.No significant differences were found between the groups on their mean age ($F_{2,80}=2.3$, $p=.25$), years of education ($F_{2,80}=1.68$, $p=.19$), or gender ($F_{2,80}=2.3$, $p=.25$). The VaD and AD patients did not differ significantly on their severity of dementia ($U=294.0$, $p=.95$), as assessed by the CDR, or mood symptoms as measured by the BDI-II ($U=257.0$, $p=.39$).

As shown by Fig. 1, no significant differences were found on the MMSE between the groups ($F_{2,80}=3.3$, $p=.15$). On the contrary, a significant difference was found on the ACE-R ($F_{2,80}=57.2$, $p<.001$), with controls outperforming both VaD ($p<.001$) and AD ($p<.001$) patients. Yet, no significant differences were found between patients with VaD and AD on the total score. Using the proposed cut-off score of 23 for the MMSE [8], a sensitivity of 42% and a specificity of 100% was obtained for the detection of cognitive impairment (AuC = 0.88, $SE=0.17$). Instead, the 88-point cut-off proposed by the ACE-R for high education populations [21] was associated with a sensitivity of 100% and a specificity of 100% (AuC = 1.0, $SE=0$). The superior discriminatory accuracy of the ACE-R relative to the MMSE showed a strong trend to significance ($z=0.95$, $p=0.09$).

In order to investigate the utility of the ACE-R in distinguishing VaD from AD patients, subscores for each subdomain were compared between these two groups. While no significant differences were found on Attention ($t_{55}=0.44$, $p=.66$), Memory ($t_{55}=-1.56$, $p=.13$), Fluency ($t_{55}=-0.39$, $p=.70$), Visuoconstruction ($t_{55}=-0.29$, $p=.77$) and Language ($t_{55}=0.19$, $p=.85$), the AD group significantly outperformed ($t_{55}=-2.61$, $p=.01$) the VaD patients on the

Table 1
Demographic and clinical profile of healthy controls, patients with vascular cognitive impairment (VaD) and patients with Alzheimer disease (AD).

	Control $n=26$		VaD $n=32$		AD $n=25$	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age (years)	73.23	8.9	75.59	6.4	77.64	5.3
Education (years)	14.46	2.2	12.97	4.3	14.48	3.6
Gender (F : M)	13:13		16:16		13:12	
CDR	–		1.15	0.8	0.91	0.2
BDI-II	1.54	1.4	7.87	6.7	5.82	4.7

CDR: Clinical Dementia Rating Scale; BDI-II: Beck Depression Inventory — II.

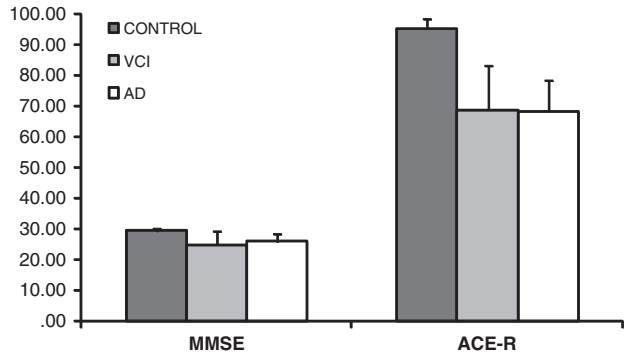

Fig. 1. Mean (*SD*) total scores on the MMSE and ACE-R.

Orientation subdomain (Fig. 2).When the fluency total score was split into its phonological and semantic fluency subscores, a trend to significance was found between VaD and AD patients on the number of animals they were able to name during one minute (semantic fluency, $t_{55} = -1.89$, $p = .06$). Within the VaD group, stronger correlations were found between the CDR and the ACE-R ($r = -.62$, $p < .001$) than the MMSE ($r = -.41$, $p < .05$).

4. Discussion

The present study demonstrates that the Spanish version of the ACE-R can be applied as a useful tool for cognitive bedside assessment in patients with subcortical ischemic vascular dementia. Moreover, the ACE-R is a better tool than the MMSE for the detection of cognitive impairments due to vascular disease. In accordance with the study using the Korean Addenbrooke's Cognitive Examination Revised [19], the total score of the Spanish version of the ACE-R revealed to have little value in the differentiation of AD and subcortical ischemic vascular dementia. These patient populations did not differ on the total ACE-R score, nor on the Attention, Memory, Fluency, Visuoconstruction and Language subscales. The only subscale that showed a differential result was the orientation subscale in which VaD patients were outperformed by the AD group. The inability of the ACE-R to distinguish between the two pathologies *in vivo* may be due to the fact that one limitation of the ACE-R is its poor capacity to detect executive dysfunction. In fact, even the original authors of the ACE mentioned its poor capability for the detection of executive dysfunction [9]. It is now known that patients who develop subcortical ischemic vascular dementia have impairments in executive functions, due to the fact that the two manifestations of subcortical cerebrovascular disease, lacunar infracts and white matter lesions occur predominantly in frontal subcortical circuits [24]. The

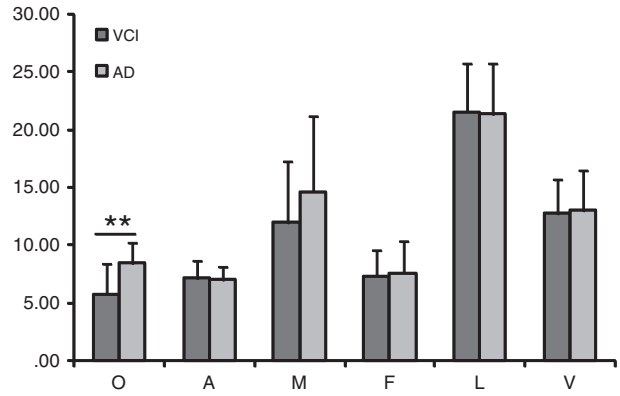

Fig. 2. Mean (*SD*) ACE-R domain subscores for AD and VAD patients. A significant difference was found for the Orientation domain (**$p = .01$). O = orientation; A = attention; M = memory; F = fluency; L = language; V = visuospatial abilities.

cognitive deficits in patients with subcortical ischemic vascular dementia can be attributed to disruption of cortical-subcortical circuits, and speed of information processing, complex attention, and frontal-executive function are likely to be affected [25]. In the case of patients with Alzheimer disease, very mild executive dysfunction may occur in some patients, but relative to vascular dementia, AD patients are not typically characterized by executive dysfunction, at least during the early stages [26]. Therefore, a proper screening battery of tests that seeks to differentiate AD from vascular dementia should address this fact and therefore include measures not only of episodic memory, but also of executive functions. In this sense, the addition of a screening tool such as the INECO Frontal Screening [27] could improve the discriminatory capacity of screening tools. The IFS is a brief, sensitive, and specific tool for the detection of executive dysfunction and we have recently showed this test is more sensitive and specific in differencing bvFTD from AD in comparison to Frontal Assessment Battery (FAB) [28], which is probably one of the most extensively used screening tools that has been design to specially asses executive functions [29–32].

Previous work validating the ACE-R into another language [19] found a trend to significance between VaD and AD patients in the semantic fluency test, indicating that the semantic fluency subtest of the ACE-R may be potentially useful in discriminating patients with VaD from patients with AD. In the Korean validation of the ACE-R for the populations, however, controls were younger than patient populations [19]. In our study, we used age-matched controls and found similar patterns. This is an important point because the verbal fluency is not only a measure of language, but also taps on executive functioning and attention, as it demands self monitoring, inhibitory control, strategy and attention. Because VaD patients' cognitive profile is typically characterized by impairments in attention and executive functions associated with involvement of frontal lobe circuits, verbal fluency may prove helpful in distinguishing this population from patients with AD.

Our study has several limitations. The participants were recruited at a specialized center. Thus, the applicability and reliability of the ACE-R in community samples require further investigation. We used the clinical diagnosis based on a comprehensive diagnostic workup and on international diagnostic criteria as the gold standard. Despite the high validity of the diagnostic criteria, clinical diagnoses are not always confirmed at autopsy. Thus, we should take into account the possibility of erroneous clinical assessments. Therefore, the validity of the ACE-R in patients with subcortical ischemic vascular dementia may be lower than our results suggest.

In conclusion, The Spanish version of the ACE-R is a brief yet reliable screening tool for the detection of cognitive impairment in patients with subcortical ischemic vascular dementia. Future studies should explore the utility of combining the ACE-R with an executive screening tests such as the IFS in their capacity to detect specific frontal-executive deficits commonly associated with VaD. While the full neuropsychological evaluation remains an extremely valuable tool in clinical practice, we suggest the ACE-R as a bedside assessment of cognitive functions in patients with vascular cognitive impairment.

Conflict of interest

No conflicts of interest reported.

Acknowledgements

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